

REVIEWER'S REPORT

Manuscript No.: IJAR-54017

Date: 24/09/2025

Title: "Ketamine Combined With Dextromethorphan-Bupropion for Depression in the Context of Nitrous Oxide Misuse"

Recommendation:

- Accept as it is
- ✓ Accept after minor revision.....
- Accept after major revision
- Do not accept (*Reasons below*)

Rating	Excel.	Good	Fair	Poor
Originality		✓		
Techn. Quality		✓		
Clarity		✓		
Significance	✓			

Reviewer Name: Dr. S. K. Nath

Date: 24/09/2025

Reviewer's Comment for Publication:

The paper provides a valuable contribution by illustrating an innovative and pragmatic approach to managing depression complicated by nitrous oxide misuse. The case underscores the potential benefits of combining rapid-acting antidepressants like esketamine with NMDA receptor antagonists such as dextromethorphan-bupropion. However, further studies with larger cohorts, longer follow-up, and objective measures are necessary to validate this strategy's efficacy and safety comprehensively.

Reviewer's Comment / Report

Strengths:

- Innovative Clinical Approach:** The paper introduces a novel therapeutic strategy involving the combined use of esketamine and dextromethorphan-bupropion to treat depression amidst nitrous oxide misuse. This approach addresses a complex clinical scenario with limited existing protocols.
- Timely and Relevant Topic:** It highlights the intersection between recreational drug misuse and emerging pharmacological treatments, which is a critical area of psychiatric research.
- Clear Case Presentation:** The case report is detailed and provides a comprehensive overview of the patient's history, treatment course, and outcomes, making it informative for clinicians facing similar challenges.
- Incorporation of Current Literature:** The authors support their approach with references to recent studies on NMDA receptor antagonists and their antidepressant effects, strengthening the rationale behind the treatment strategy.

Weaknesses:

- Limited Generalizability:** As a single-case report, the findings cannot be generalized. The paper would benefit from discussing limitations regarding broader applicability and the need for larger studies.
- Insufficient Long-term Follow-up:** The follow-up period described is only two weeks, which is short for assessing sustained remission and abstinence in substance misuse contexts.
- Lack of Objective Metrics:** The report references clinical improvements but does not specify standardized scales (e.g., MADRS, HAM-D) used objectively to measure depressive symptoms pre- and post-treatment.
- Absence of Biological or Neurochemical Data:** The paper discusses potential mechanisms but does not include any neurobiological or biochemical assessments to substantiate the pharmacological claims.
- Minor Editorial Errors:** There are some grammatical inconsistencies and typographical errors throughout the manuscript that could hinder readability.

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Recommendations for Improvement:

1. **Expand on Limitations:** Clearly acknowledge the limitations inherent in case reports and suggest future research directions, including larger sample sizes and controlled trials.
2. **Include Objective Measures:** Incorporate standardized depression rating scale scores pre- and post-intervention for more precise assessment.
3. **Discuss Long-term Outcomes:** Provide insights into sustained effects and relapse prevention strategies beyond the short-term follow-up.
4. **Enhance Language and Grammar:** Review and correct grammatical errors and improve sentence clarity for better readability.
5. **Add a Biological Perspective:** If possible, include or suggest neurobiological or biomarker data to support the proposed mechanisms.

Editorial Corrections:

- Ensure consistency in referencing (some references seem misnumbered or incomplete).
- Check for minor grammatical issues, such as punctuation and sentence structure.
- Clarify abbreviations on first use (e.g., MADRS, TRD).
- Confirm all references are appropriately cited and formatted uniformly.